Regulation of Assisted Conception: UK experience

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Regulation of assisted conception

History

Warnock Committee

Human Fertilisation and Embryology Authority

Laboratory to clinic

USA : UK

Co-operative Research on the Development of The Early Human Embryo

History

1978: Birth of first ‘test-tube’ baby

1984: Warnock Report

1985: Voluntary Licensing Authority

1989: Interim Licensing Authority

1990: Human Fertilisation and Embryology Act

1991: Human Fertilisation and Embryology Authority (HFEA)

The Warnock Report

Committee of Inquiry into Human Fertilisation and Embryology (1982-1984)

"To consider recent and potential developments in medicine and science related to human fertilisation and embryology; to consider what policies and safeguards should be applied, including consideration of the social, ethical and legal implications of these developments; and to make recommendations."

Warnock Report: Regulating infertility services and research

"We therefore recommend the establishment of a new statutory licensing authority to regulate both research and those infertility services which we have recommended should be subject to control."

The status of the early human embryo

Morality is “more properly felt than judg’d of”

(Hume: Treatise of Human Understanding 1738)

“According to the majority view, the question was not, as is often suggested, whether the embryo was alive and human, or whether, if implanted, it might eventually become a full human being. We concluded that all these things were true. We nevertheless argued that, in practical terms, a collection of 4 or 16 cells was so different from a full human baby, or a fully formed foetus, that it might quite legitimately be treated differently. Specifically, we argued that, unlike a full human being, it might legitimately, be used as a means to an end that was good for other humans” (Warnock, 1985).

The status of the early human embryo

The value placed on the embryo "is really determined not by specific criteria that could be applied to determining the inherent value of the embryo, since there's so much disagreement about that, but rather by the value that all of us who have been born and thought about this have placedon the embryo" (Alta Charo in RM Green *The Human Embryo Research Debates*, 2001 Oxford University Press)

"In a pluralistic society, you strive to respect the views of others, including those with whom you disagree. One should try to minimize their moral 'pain' as much as possible while not relinquishing vital social objectives" (RM Green)

Human Fertilisation and Embryology Authority (HFEA)

Medical intervention or research which aims to alleviate infertility of reduce the risk of inherited abnormality intrudes upon the most private and sensitive aspects of our existence and relationships.

The HFEA was established in response to deep public concern about the implications which the new techniques might have for the perception and valuing of human life and family relationships.

The HFEA Act - -

‘governs bringing about the creation of an embryo outside the human body’

Human Fertilisation and Embryolgy Authority

21 members – majority are lay people – appointed by the Government following open recruitment

Executive – about 60 people

Budget – about $6m per ann

25% from government

75% from patients

Prohibitions of the HFE Act

No person can use / store, create an embryo without a licence

No person can store gametes without a licence

No person can mix human & animal gametes without a licence

No person can use / store an embryo after the appearance of The primitive streak and / or 14 days after fertilisation

No person can replace a nucleus of a cell of an embryo with a nucleus taken from a cell of any person, embryo or subsequent development of an embryo

HFE Act

'The Authority shall maintain a Code of Practice'

- Staff (The Person Responsible)
- Facilities
- Assessing people seeking treatment and considering donation
- Information and consent
- Counselling
- Research
- Records

Licensing and Regulation

Annual Inspection

- Facilities: clinical, laboratory, nursing, counselling
- Paperwork: patient information / clinic protocols
- Compliance with the Code of Practice

Report to Licensing Committee

3-year Licence normally granted

HFEA requirements

Only two, exceptionally, three, embryos may be transferred in any given treatment cycle

Success rates must be expressed as:
Live birth rate per treatment cycle started

Multiple births

Still birth and neonatal deaths per thousand birth events

Singleton	9.9
Twin	43.8
Triplet	59.6

Multiple births

"A generation of children with birth-related cerebral palsy, mental retardation and severe respiratory or digestive problems is a little-noted consequence of the practice of infertility medicine and the ban on human embryo research"
(R M Green, 2001)

Novel aspects of HFE Act

- Consent
- Information
- Counselling
- Confidentiality
- Welfare of the Child

"A woman shall not be provided with treatment services unless account has been taken of the welfare of any child who may be born as a result of the treatment (including the need of that child for a father), and of any other child who may be affected by the birth"

HFE Act (1990) Section 13 (5)

Welfare of the Child

Social and psychological well-being

Physical well-being

Health of the Child

Efficacy and safety in ART

Licensing of Research

To promote advances in the treatment of infertility

To increase knowledge about the causes of congenital disease

To increase knowledge about the causes of miscarriages

To develop more effective techniques of contraception

To develop methods for detecting gene or chromosome abnormalities in embryos before implantation

Criteria for human embryo research

- Importance of the research
- Whether the research has been done before
- Whether use of human embryos is justified
- Suitability of methods
- Length of study
- Applicant's qualifications

New developments in ART

Laboratory to clinic: the conventional route

1. Experiments on cells and tissues (animal / human), whole animals, human volunteers
2. Pre-clinical trials
3. Prospective Randomised Controlled Trials
4. Meta-analyses
5. Clinical Practice
6. Evaluation (in the UK) by the National Institute of Clinical Excellence (NICE)

RCOG Study Group on Fetal Programming

"Advances in assisted conception techniques are being introduced into the clinic before the basic scientific work on how they affect early embryonic development has been carried out. This situation should be reversed. All babies born after assisted reproductive technologies should be followed-up into middle age and biological records kept of their health"

"Before new assisted-reproduction techniques are adopted as routine treatment for infertility, they should be assessed extensively in animal and human embryo research, then in clinical trials, during which the children must be monitored long term."

te-Velde et al, Lancet, **351**, 1524, 1998

Health Council of the Netherlands (1998)

‘New methods and techniques in the field of artificial reproduction are sometimes tested in humans without adequate preclinical research in animals (for possible harmful effects, including longer term effects and effects spanning several generations). Any possible safety hazards are thus shifted to the woman and to the child’

‘Under no circumstances whatsoever may women and children be turned into trial subjects for the sake of protecting embryos’.

Push > > Medical Progress >> Pull

Basic Science

Patients' needs

New Techniques

Economics

Animal models

Invertebrates

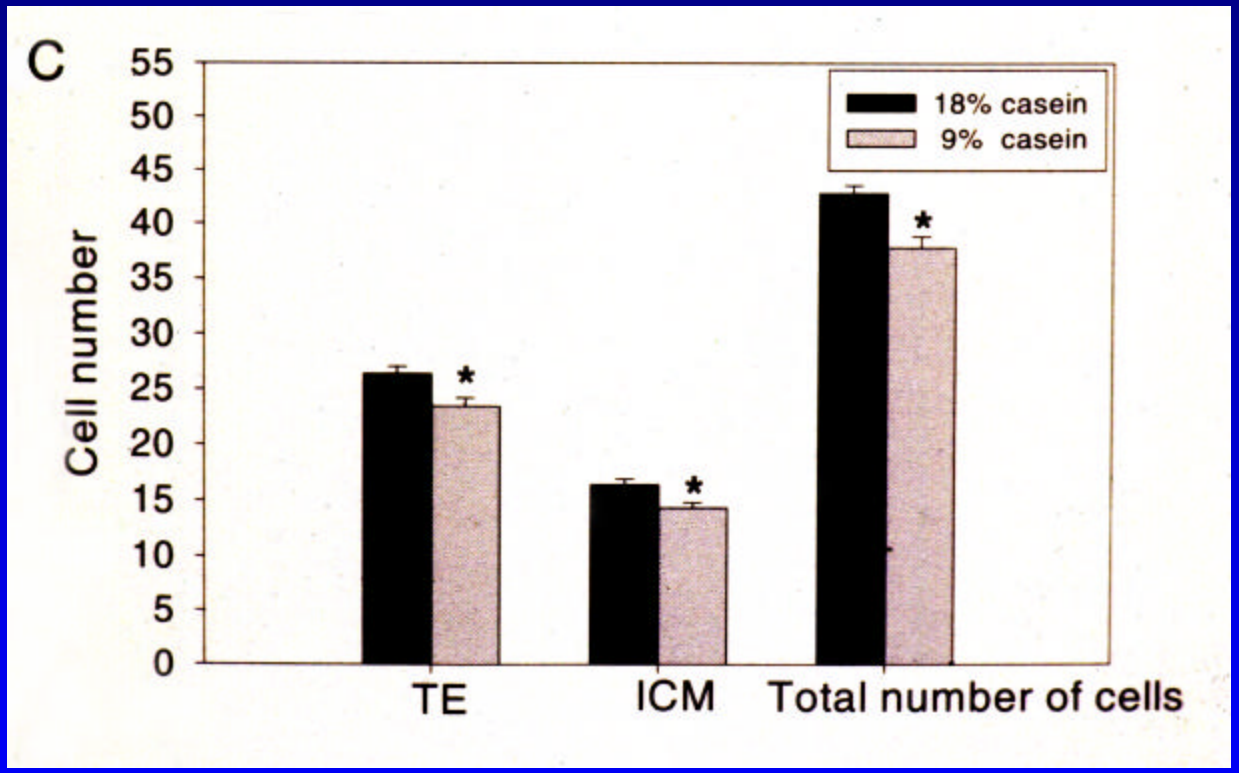
Rodents

Domestic animals

Non-human (lower) primates

Effect of maternal low protein diet during 0-4.25 days of pregnancy on blood pressure in adult offspring (mice).

	18% protein		9% protein	
	Male	Female	Male	Female
Systolic blood pressure (mm Hg)	106	135	115	142


C
Cell number
55
50
45
40
35
30
25
20
15
10
5
0
18% casein
9% casein
*
*
*
TE
ICM
Total number of cells

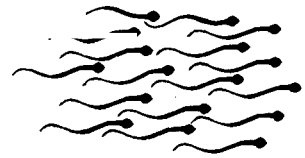
Dissect intact follicles

Ovary dissection

Oocyte-cumulus complex

In vitro maturation

In vitro fertilization

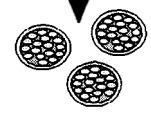


Inseminate

In vitro

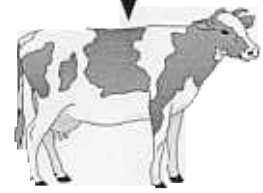
Embryo culture

Blastocysts for evaluation, freezing



or

Transfer to recipients



Stages in embryo-based technologies as potential targets for external agents

- Ovarian stimulation
- In vitro maturation of gametes
- In vitro fertilization / ICSI
- Somatic cell nuclear transfer
- Embryo culture: prolonged; use of serum; co-culture with somatic cells
- Implantation: asynchrony between embryo and uterus; altered hormonal milieu
- Physical agents: micromanipulation

Some phenotypic consequences of early exposure of embryos to external agents

- Deviation in inner cell mass/trophectoderm cell numbers
- Altered metabolism during organogenesis
- Fetal/perinatal abnormalities and loss
- Large Offspring
- Deviations in allometric coefficients in adult tissues
- Elevated blood pressure/glucose intolerance in adult offspring

Characteristics of preimplantation embryo development

- The egg is the largest cell in a woman's body
- *Eggs and embryos are relatively autonomous and have astonishing regulative powers* (Anne McLaren, 1976)
- In the human, almost all our knowledge is derived from studying eggs and embryos *in vitro* – there are no *in vivo* controls

Conclusions:

1. Most recent advances in human assisted conception have arisen from the development of new techniques rather than from advances in basic science.
2. We rely on the resilience of the egg and early embryo to survive the physical and chemical manipulations used in fertility treatments.
3. The evidence-base is weak.
4. More research is needed.

Animal models

Mouse	Cow	Pig	Primate
Pro:			
Genetics	IVP	IVP	Closest to
ET	'human'	large litters	human
In vivo	metabolism	genotyping	*In vivo*
Con:			
Small size	Prolonged	Lipid stores	Ethics
Too efficient!	pre-attach	Prolonged	Availability
		pre-attach	Lack of info

HFEA decision-making: Working Group on New Developments in Reproductive Technology

1. Assessment of literature
2. Expert opinion
3. Consultation with professional bodies and practitioners
4. Referral to HFEA sub-committees (eg Ethics; Code of Practice; Licence & Fees)
5. Public consultation (eg sex pre-selection / fetal ovarian tissue / preimplantation genetic diagnosis / stem cell therapy)
6. Authorisation by the Authority
7. Clinical / Research Licences granted by Licence Committee
8. Monitoring of outcome – review of policy

Novel Techniques in ART

Allowed:

Egg freezing and thawing

Screening for aneuploidy

IVF / ICSI following *in vitro* maturation of oocytes

HLA tissue typing / PGD

Human Embryonic Stem Cell generation

Novel techniques in ART

Disallowed:

ICSI with elongated or round spermatids

Fragment removal

Cytoplasmic transfer

Stem cells

1997 ‘Dolly’

1998 Isolation of human ES cells

1998 HFEA / HGAC Public consultation

1999 DoH, DTI, OST response

2000 DoH report; Nuffield; Royal Society

2000 Parliamentary vote 366>174 in favour

2002 House of Lords Select Committee

2002 First HFEA licence under new purposes

Stem cells offer hope

'- - - underpinned by the considerable confidence which has been generated by the effective and strict regulation of all embryo research by the HFEA in the last decade'

The Guardian 18/11/2000

USA : UK

'Pro-life' movement extremely active in USA

– *little influence in practice in UK*

Strong 'pro-science' lobby in UK

– *recognised that science could be protected by legislation*

Difficult to frame US-wide legislation - Federal vs State Laws

- *legislative power of HFEA together with lay-control*

Strong commercial drive in US clinics

US accreditation / monitoring is professionally driven

Federal funding of embryo research

"The USA - - relies less on the stick than the carrot and its system of regulation is highly decentralized and multifaceted. Instead of passing national laws prohibiting activities, the federal government holds out the conditional offer of financial support"

"Given our extreme differences of opinion on matters relating to the beginning and end of life and genetic interventions, a centralized, law-based system of research Regulation would inevitably become hostage to our political differences" (R M Green, 2001).

Federal funding of embryo research

"It is irresponsible for a modern society fo permit the widespread provision of medical services without simultaneously fostering the research needed to establish the efficacy and safety of those services. In addition, a pluralistic democracy committed to protecting and improving the health of its citizens cannot justly deny one area research support merely because some of its citizens object to that research on the basis of their personal religious and moral beliefs"

(R M Green, 2001)

European legislation on embryo research

Germany: not allowed

France: allowed exceptionally on ‘spare’ embryos

Denmark: allowed up to 14 days after fertilisation

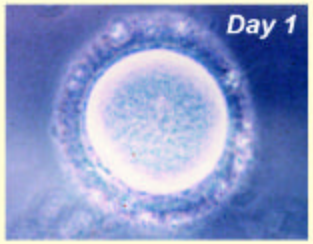
Norway: not allowed

Sweden: allowed up to 14 days after fertilisation

UK: allowed up to 14 days after fertilisation – only country which allows creation of ‘research’ embryos

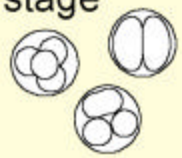
UK Medical Research Council Co-operative on the Development of the early human embryo

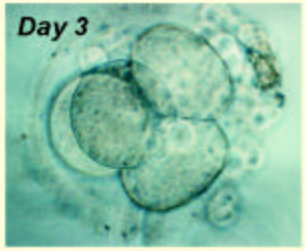
HJ Leese, FD Houghton, DR Brison, TP Fleming, SJ Kimber & HM Picton



fertilized pronucleate eggs

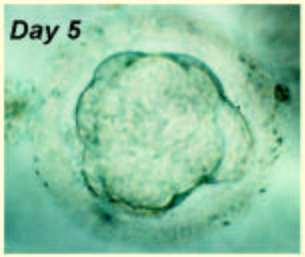
2- to 4-cell stage



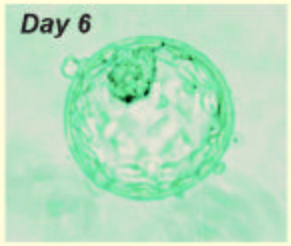


8- to 16-cell stage

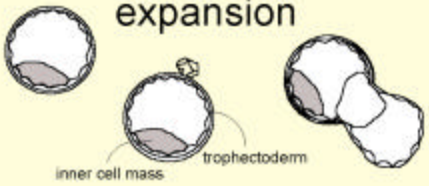
compaction and morula formation



cavitation



blastocyst formation and expansion



- We know rather little about the biology of the early human embryo due to the small numbers of surplus embryos available for research, and their generally poor quality.
- There are few markers of normal preimplantation human embryo development

Hypothesis:

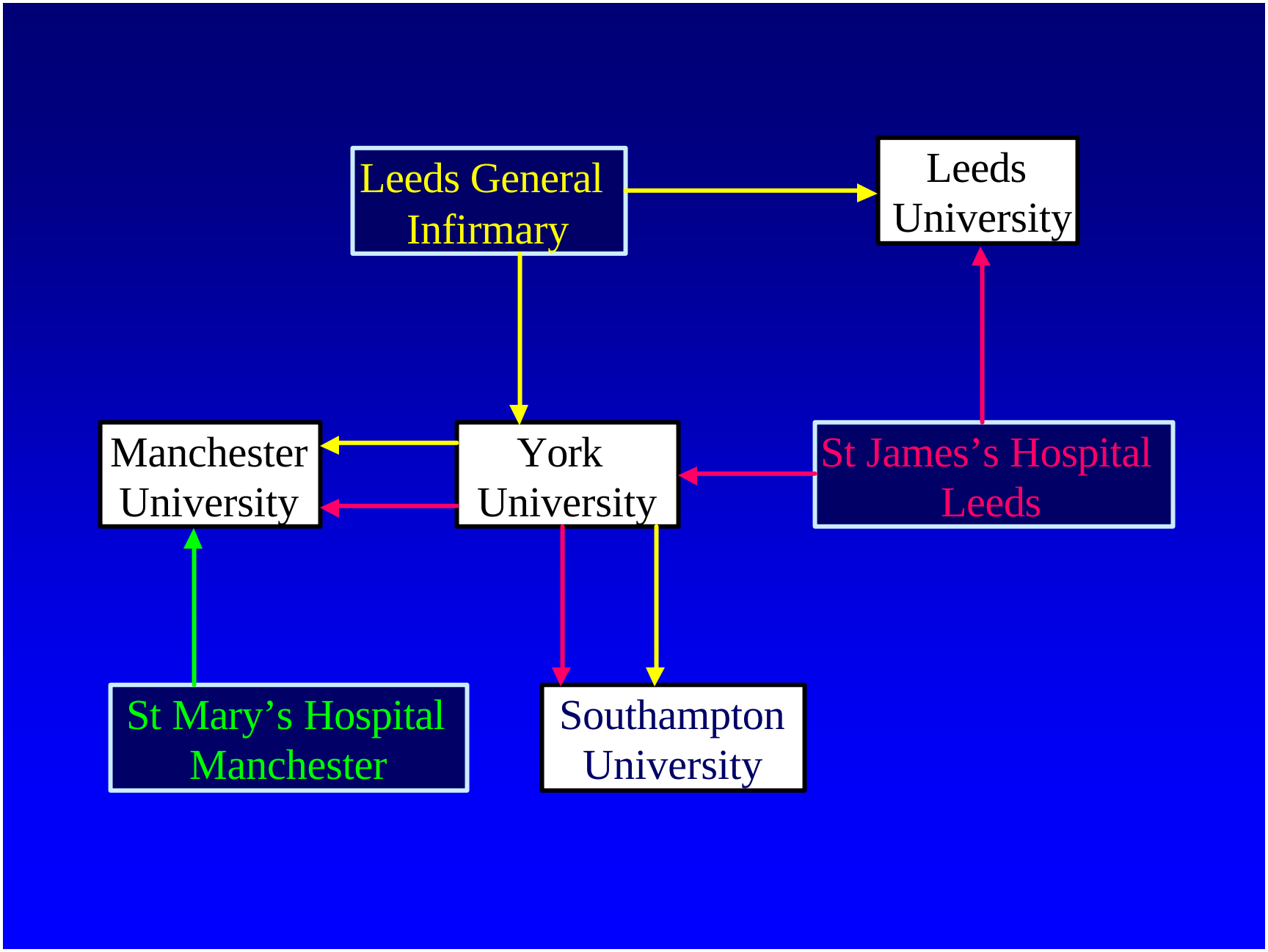
To form a viable human blastocyst requires the activation of a developmental programme comprising:

- Generation of chromosomally/genetically normal blastomeres
- Gene expression of key markers of development
- Elimination of blastomeres by apoptosis
- Biogenesis of epithelial intercellular junctions
- Metabolic differentation and appearance of vectorial transport

Strategy

To maximise use of a precious resource: the early human embryo

To perform dual analyses on single embryos


Leeds General Infirmary
Leeds University
Manchester University
York University
St James's Hospital Leeds
St Mary's Hospital Manchester
Southampton University

Leeds Research-Molecular Investigation of the development of human embryo *in vitro*

1. Interphase FISH

Genetics of the early cleavage embryo-chromosome analysis for common aneuploidies and mosaicism rate

2. Metaphase FISH

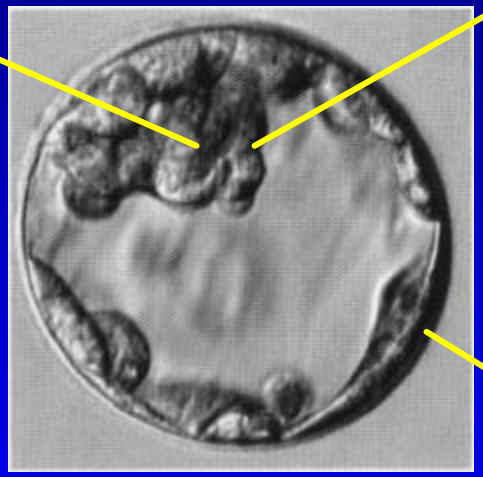
Karyotype analysis of human Metaphase II oocytes

Karyotype analysis of blastomeres in parallel with interphase FISH

Single embryo gene expression profile

Inner Cell Mass:
Genetic markers of pluripotency, proliferation & differentiation

Apoptosis



Zygotic genome activation

Trophectoderm: markers of epithelial cell differentiation

Markers of metabolic stress

Growth factors and receptors

Signal transduction Molecules

Establishment of the junctional seal in human embryos

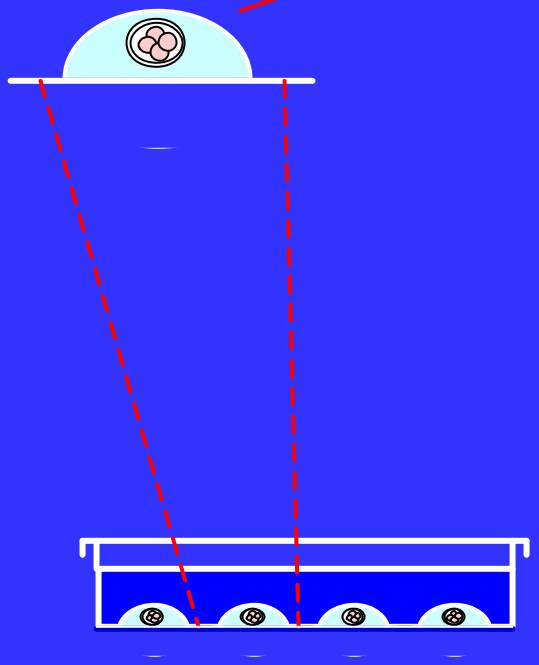
Aims:

to analyse gene expression and membrane assembly of junctional proteins in human embryos

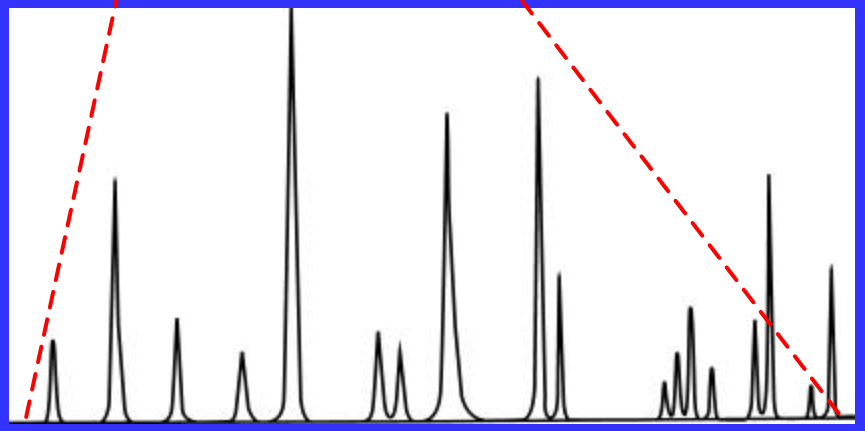
1. **Screening of individually staged and graded embryos for the presence or absence of mRNA expression of genes associated with intercellular junctions during blastocyst formation by RT-PCR**
2. **Examination of junctional protein expression in human embryos by immunolabelling and confocal microscopy**

Amino acid analysis by high pressure liquid chromatography (HPLC)

Sample of medium taken for analysis

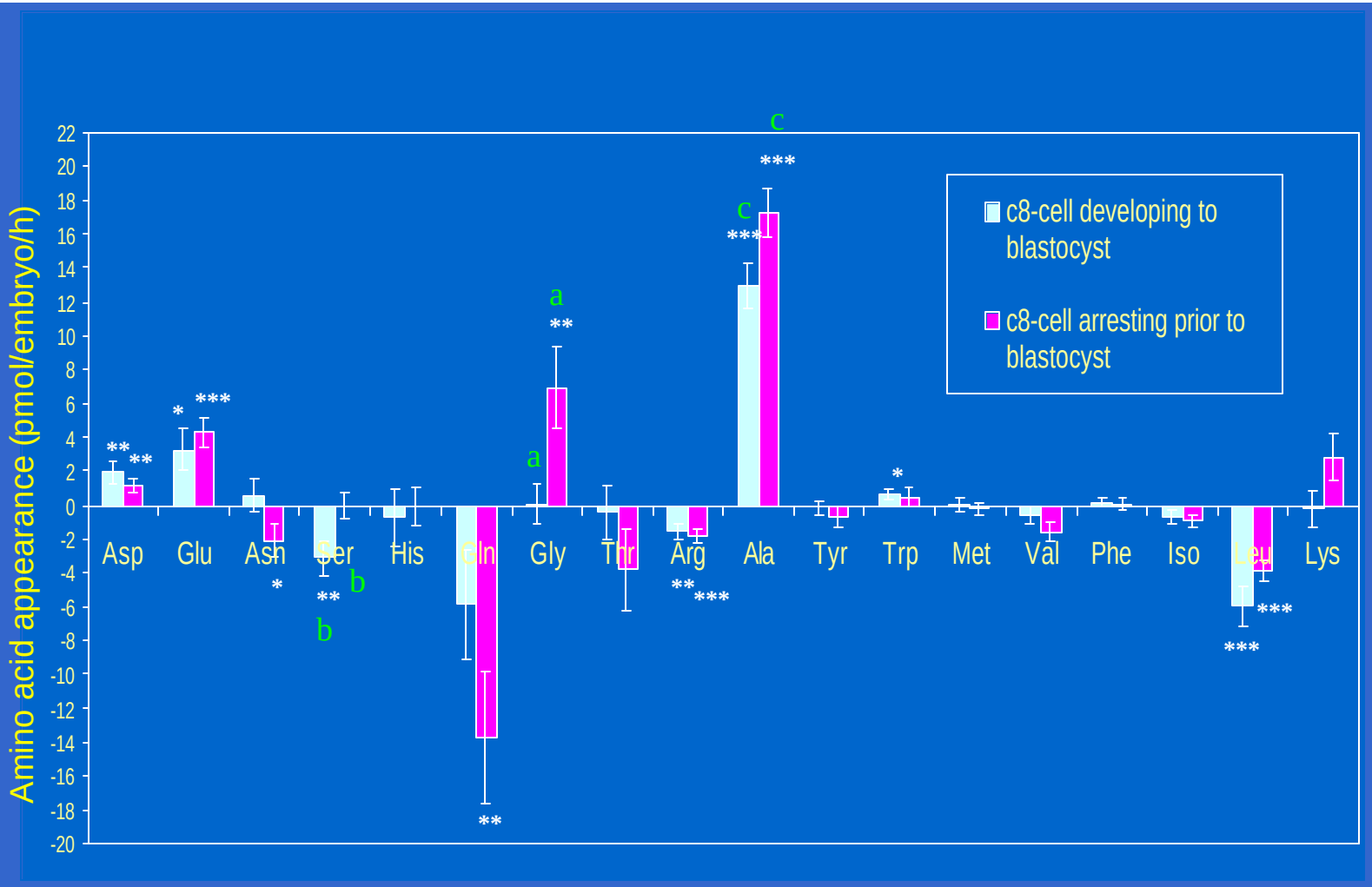


Embryos cultured singly in microdrops under oil for 24h

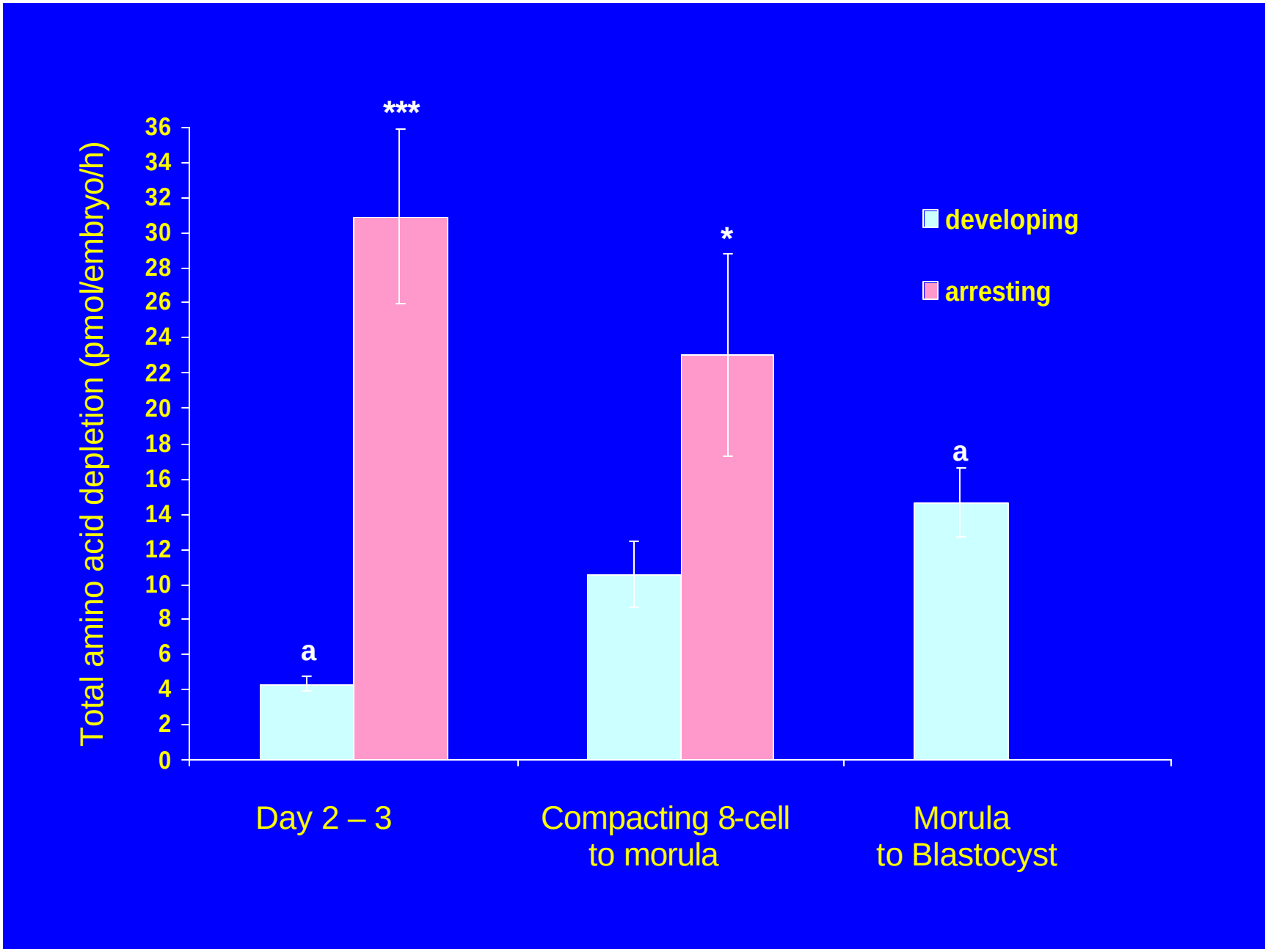


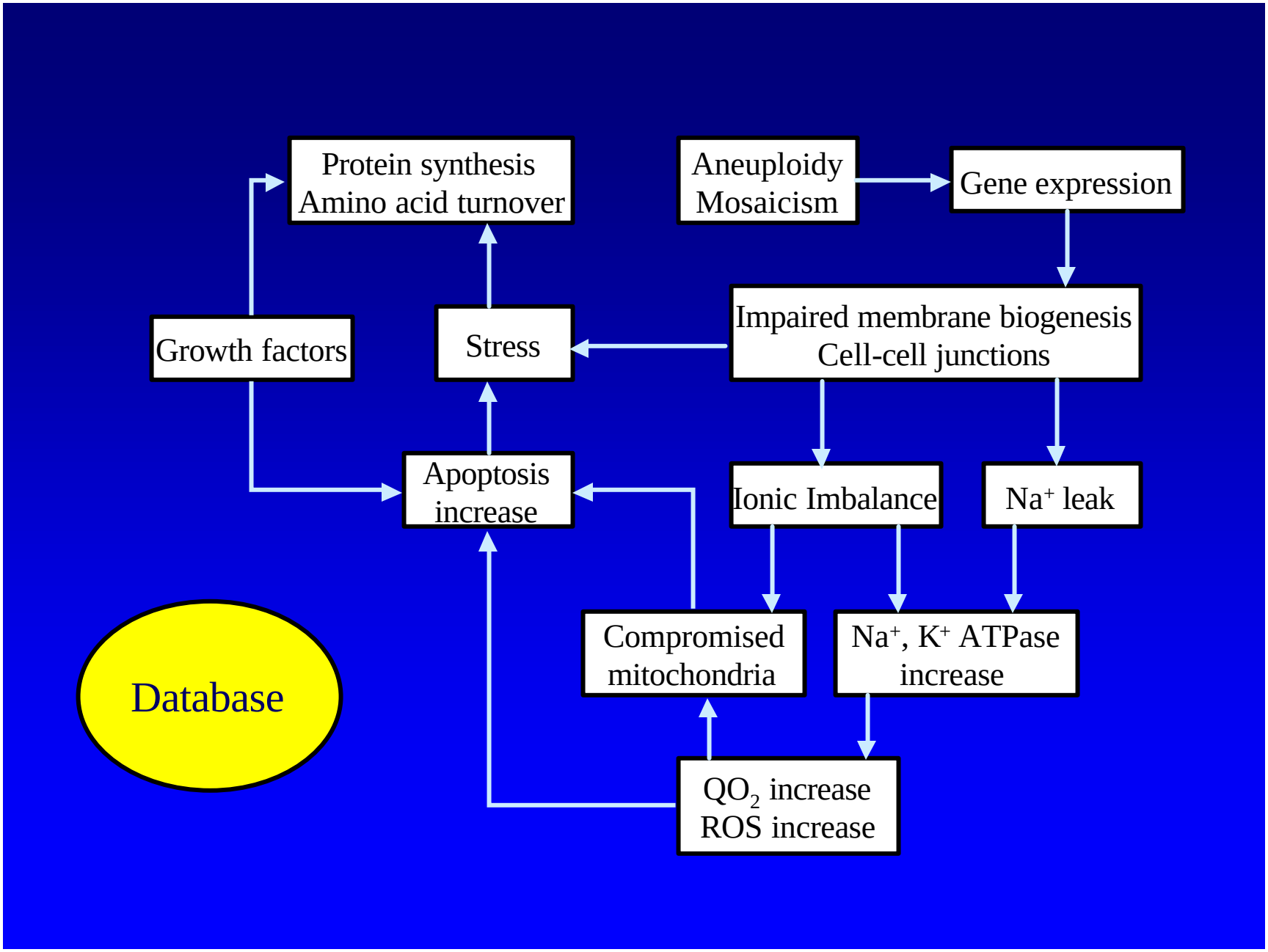
Embryo amino acid profile

Amino acid profile determines embryo health



a, *P*=0.015; b, *P*=0.019; c, *P*=0.037.


Total amino acid depletion (pmol/embryo/h)
36
34
32
30
28
26
24
22
20
18
16
14
12
10
8
6
4
2
0
***
*
a
a
developing
arresting
Day 2 – 3
Compacting 8-cell
to morula
Morula
to Blastocyst


Protein synthesis
Amino acid turnover
Aneuploidy
Mosaicism
Gene expression
Growth factors
Stress
Impaired membrane biogenesis
Cell-cell junctions
Apoptosis
increase
Ionic Imbalance
Na+ leak
Database
Compromised
mitochondria
Na+, K+ ATPase
increase
QO2 increase
ROS increase

Some websites

Human Fertilisation and Embryology Authority
www.hfea.gov.uk
UK Department of Health – stem cell research
www.doh.gov.uk/cegc
UK Human Genetics Commission
www.hgc.gov.uk
Nuffield Council on Bioethics
www.nuffieldfoundation.org.bioethics
The Royal Society
www.royalsoc.ac.uk
National Institutes of Health – Stem cells: a primer
www.nih.gov/news/stemcell/primer.htm
House of Lords report on Stem Cell Research
www.parliament.the-stationery-office.co.uk/pa/ld/ldstem.htm